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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#18/E.O.T. 4 mos

In re Application of	
John J. ROSSI, *et al.*	
Serial No. 09/465,925	Examiner: A. Wang
Filed: December 17, 1999	Group Art Unit: 1635
For: INHIBITORS AND TARGET MOLECULE CO-LOCALIZATION	

TRANSMITTAL OF APPEAL BRIEF

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed in connection with the above-referenced application is an Appeal Brief with Appendix in triplicate. A check in the amount of $885 is enclosed to cover the following fees: $160 to cover the fee for filing a brief in support of a notice of appeal and $725 to cover four months of extension of time.

Also, please charge any additional fees or credit any overpayment to Deposit Account No. 02-2135. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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#18/R.T. 5/9

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Appeal Brief

APPELLANTS' BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is an appeal from the May 2, 2002 final Office Action rejecting claims 1, 3-5, 8 and 9 in the above-identified application.

REAL PARTY IN INTEREST

The present application is assigned to the City of Hope, Duarte, California.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to appellants or the appellants' legal representative which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 2 and 6-7 have been canceled. Claims 1, 3-5, 8 and 9 are all the remaining claims in the application, and on appeal.

STATUS OF AMENDMENTS

There have been no amendments filed subsequent to the May 2, 2002 final rejection.

SUMMARY OF INVENTION

The invention relates generally to mechanisms for bringing two or more molecules together in a living cell. More particularly, the invention relates to mechanisms for bringing together within a cell a target molecule and an inhibitor to the target so as to increase the concentration of the inhibitor with respect to the target. One embodiment of this invention relates to chimeric $tRNA^{Lys}$-ribozyme constructs which compete effectively with $tRNA^{Lys}$ for binding to HIV-1 reverse transcriptase. These chimeric molecules provide a co-localization mechanism for delivering inhibitors of HIV-1 and reverse transcriptase to the virion particle itself.

Claim 1 defines a process in which an RNA target molecule and a ribozyme inhibitor for the target molecule

are positioned within a cell such that the concentration of the inhibitor relative to the RNA target is enhanced. Claim 3 specifies that the target is an HIV-1 RNA molecule, and the inhibitor cleaves that RNA molecule.

Claim 5 recites a living cell in which and RNA target and a ribozyme inhibitor have been co-localized. Claim 8 recites a specific co-localization method in which the ribozyme inhibitor includes (i) the dimerization or packaging signal of said RNA target molecule, or (ii) a sequence capable of pairing with said RNA target molecule at a site upstream of a $tRNA_3^{Lys}$ binding site on said RNA target molecule wherein said ribozyme is bound to a $tRNA_3^{Lys}$ molecule at the 3' end of said $tRNA_3^{Lys}$, or (iii) a 3' untranslated region (UTR) of said RNA molecule, or (iv) a sequence capable of binding to a cellular protein to which the target RNA also binds, or (v) a sequence capable of binding to a unit of a multimeric cellular protein such that the target RNA binds to the same or another unit of the multimer. Claim 9, which depends from claim 8, specifies that the target is an HIV-1 RNA molecule.

THE REJECTIONS

All claims are rejected under 35 USC §112, first paragraph, for alleged lack of enablement of the specification.

All claims are rejected under 35 USC §102(b) as being anticipated by Sullenger, *et al.* (*Cell* 63, pp. 601-608, November 1990).

All claims are rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1-19 of U.S. Patent No. 5,827,935.

ISSUES

I) Whether the specification provides an enabling disclosure for the claims on appeal.

II) Whether the Sullenger (*Cell*) reference anticipates the claims on appeal.

GROUPING OF CLAIMS

Separate argument is made for each claim.

ARGUMENT

I. The Specification Provides an Enabling Disclosure

The final rejection under 35 USC §112, first paragraph, seems to be based on the contention that the specification

does not enable the full scope of the claims. In particular, the Action seems to contest that *in vivo* methods are enabled. That is incorrect.

All of the claims on appeal recite methods in which concentration enhancement or co-localization between an RNA target and an inhibitor takes place within a living cell. The Examiner does not dispute that the specification provides guidance and examples demonstrating the claimed processes in living cells, but apparently views that as limited to *in vitro* application. However, the Examiner fails to provide any basis for doubting that the methods taught in the specification have applicability in what the Action considers to be *in vivo* use. The specification discloses a number of methods, including viral mediated delivery (page 31, lines 21-23). The level of skill in the art is obviously quite high, and there is no evidence presented by that such a delivery system would not work in an *in vivo* setting.

Moreover, the references cited in the Action simply do not support the rejection, and the Action attributes to them an unwarranted level of importance. Agrawal, Gewirtz and Branch are all review articles which do not purport to advance any new and original research. Instead of

establishing doubt as to *in vivo* use, they each report encouraging uses of the technology described in each paper.

For example, Agrawal states that:

> Over the past 2-3 years, many reports have appeared in the literature confirming the application of antisense technology in *in vivo* models . . .

Numerous reports are summarized (p. 376). Similarly, Gewirtz reports that "several [oligodeoxynucleotide] reagents have reached clinical trials for a variety of indications, including leukemia, cancer, and AIDS" (p. 3161). Branch states that "there is growing evidence that antisense molecules can be useful pharmacological tools when applied carefully" (p. 50).

While each article does discuss the difficulties inherent in the field, they are cited as part of an academic discussion of practical considerations in the field. But the fact that certain things must be considered when designing drugs does not mean that they are insurmountable problem evidencing lack of enablement. The proper legal test is not whether *any* experimentation is necessary, but rather whether *undue* experimentation is necessary. *See, Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The articles relied upon are evidence that one of ordinary skill would be given considerable guidance by

the art, and the Action fails to meet the PTO's burden of proving lack of enablement. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); MPEP §2164.04.

In addition, each of the references relied on by the Examiner was published after the claimed priority date of the present application. Therefore, the Examiner's reliance on them runs afoul of MPEP §2164.05(a) which states that:

> In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling.

Because the references are not directed to what one of ordinary skill would have understood as of the present effective filing date about co-localization between RNA targets and ribozyme inhibitors in general (claims 1 and 4); or HIV-1 RNA molecules and ribozymes which cleave such RNA (claims 3 and 9); or ribozymes including the specific elements recited in claim 8; or cells in which an RNA target and a ribozyme inhibitor have been co-localized (claim 5), they are irrelevant.

For the foregoing reasons, the rejection under 35 USC §112, first paragraph, should be reversed.

II. The Sullenger Reference Does Not Anticipate the Claims on Appeal

The Sullenger paper reports work in which chimeric $tRNA^{met}$-TAR transcription units were used to express high levels of HIV-1 TAR-containing transcripts, which were said to inhibit HIV-1 replication. The Examiner appears to rely heavily on the statement bridging the columns on page 605 as establishing co-localization, but that statement does not prove the Examiner's point. To the contrary, Sullenger (*Cell*) states that "[t]he intracellular localization of the tRNA-TAR fusion transcripts *was not determined*" (emphasis added). The subsequent observations regarding the work of others is nothing but speculation, and there is nothing in the Sullenger paper which would lead one of ordinary skill to believe that concentration enhancement or co-localization actually occurred. Therefore, Sullenger (Cell) cannot anticipate claims 1 and 2, which require concentration enhancement by positioning; or claims 4, 8 or 9, which recite methods for co-localization; or claim 5, which recites a living cell in which and RNA target and a ribozyme inhibitor for the target are co-localized.

In addition, Sullenger's inhibitor (the tRNA-TAR fusion transcript) is a TAR decoy, and not a ribozyme. Because each claim on appeal recites that the inhibitor is a

ribozyme, Sullenger cannot anticipate for that additional reason.

Moreover, there is no disclosure in Sullenger that its inhibitor cleaved the RNA target molecule, as recited in claims 3, 8 and 9. Therefore, Sullenger cannot anticipate those claims for that additional reason.

For the foregoing reasons, the rejection under 35 USC §102(b) should be reversed.

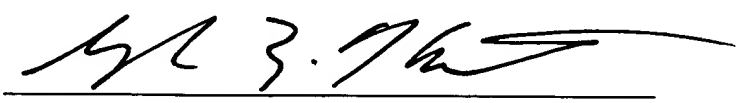
III. The Double Patenting Rejection

With respect to the double patenting rejection in view of U.S. Patent 5,827,935, a terminal disclaimer will be submitted upon an indication of allowable subject matter.

CONCLUSION

For the reasons stated above, Appellants respectfully request the reversal of the rejections under 35 USC §§112 and 102(b).

Respectfully submitted,



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APPENDIX

COPY OF CLAIMS ON APPEAL

1. A process which comprises the positioning, within a living cell, of an RNA target molecule and a ribozyme inhibitor for said target molecule, said positioning being such that the concentration of the inhibitor molecule with respect to the target molecule is enhanced.

3. The claim 1 process in which the target molecule is an HIV-1 RNA molecule and the inhibitor is a ribozyme which cleaves said HIV-1 RNA molecule.

4. A method which comprises co-localizing an RNA target molecule and a ribozyme inhibitor for said target molecule within a living cell.

5. A living cell in which an RNA target molecule and a ribozyme inhibitor for said target molecule are co-localized.

8. A method which comprises co-localizing within a living mammalian cell

an RNA target molecule, and

a ribozyme which cleaves said RNA target molecule said ribozyme including

(i) the dimerization or packaging signal of said RNA target molecule, or

(ii) a sequence capable of pairing with said RNA target molecule at a site upstream of a $tRNA_3^{Lys}$ binding site on said RNA target molecule wherein said ribozyme

is bound to a $tRNA_3^{Lys}$ molecule at the 3' end of said $tRNA_3^{Lys}$, or

(iii) a 3' untranslated region (UTR) of said RNA molecule, or

(iv) a sequence capable of binding to a cellular protein to which the target RNA also binds, or

(v) a sequence capable of binding to a unit of a multimeric cellular protein such that the target RNA binds to the same or another unit of the multimer.

9. The claim 8 method in which said RNA target molecule is an HIV-I RNA molecule.